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REVIEW ARTICLE

Breast Cancer Genes and the Surgeon

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Two genes, called BRCA-1 and BRCA-2, have been identified that appear to be responsible for the majority of familial breast cancer syndromes. These genes now play a prominent role in the practice of the surgeon treating breast cancer. Additional genes, PTEN (Cowden disease), MSH1 or MLH2 (HNPCC), and p53 (Li-Fraumeni syndrome) are responsible for other breast cancer syndromes but have not yet entered the clinical arena on a large scale. The risk of breast and ovaran cancer by age 70 in a BRCA-1 mutation carrier is estimated at 55–75% and 16–26 %, respectively, overall, and as high as 87% and 44% in those with a strong family history. The cancer risks associated with BRCA-2 mutations appear to be somewhat lower than those of BRCA-1. BRCA mutations show a strong founder effect. This is best recognized in the Ashkenazi Jewish community, in which the incidence of one of three characteristic mutations is about 2%. In other ethnic groups the pattern of mutations is different, with over 100 distinct mutations throughout the genes having been described. Most mutations so far have been frame-shift or mis-sense mutations, although large deletions have also been described. Thus, in most situations, assessment of the whole coding sequence is required to confirm or exclude a mutation. Guidelines to suggest who is likely to be a mutation carrier are being clarified, but the appropriate management of someone who tests positive remains difficult. Prophylactic mastectomy and oophorectomy are likely to offer substantial gains in life expectancy to mutation carriers, especially for young women with a strong family history. Unfortunately, there are no currently available strategies to eliminate the risk of breast or ovarian cancer. The psychological impact of testing also remains poorly understood, and the danger of various forms of discrimination remain. These factors must be clearly understood by all parties prior to testing. The process of a dynamic, interactive informed consent—much more than a simple printed document—and also counseling are central to the testing process *J. Surg. Oncol. 1998;67:267–274.*

KEY WORDS: breast cancer; heredity; genetic testing; surgery

INTRODUCTION

Breast cancer is a genetic disease. Fundamentally, breast cancer cells are defined by their genetic composition and it is likely that the lethality of a particular tumor is a manifestation of that tumor's accumulated genetic damage. The net effect of a complex interplay among cancer causing-genes (oncogenes), tumor suppressor genes, cell cycle regulatory genes, and DNA repair genes is a growth advantage to the cancer cell. Molecular bi-

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ology is gradually revealing the intricacies of the cancer cell. Predicting the behavior of a tumor based on its molecular characteristics is a major research goal but does not have wide clinical application at present. Genetic testing for breast cancer susceptibility, however, is now available for some women.

It is typically the surgeon who supplies initial information, advice, and support to a person with breast cancer. The rapid development of clinical cancer genetics means that it is increasingly important for those treating breast cancer to have an understanding of this field. The surgeon must have a firm grasp of the underlying theory, and more importantly must clearly understand the promise and pitfalls that accompany this new information. This is the focus of this review.

BACKGROUND

Familial clustering of breast cancer has been recognized since Roman times. Possible explanations include not only genetic predisposition but also shared environmental and cultural risk factors. The earliest reported acknowledgment of familial clustering appeared in the modern literature in 1866, when a French surgeon reported multiple cases of breast cancer in four generations of his wife's family [1]. Today, only about 10% of patients with a newly diagnosed breast cancer are aware of a family history of the disease [2–4]. It is worth noting that most people only know one or two generations of family history, so the true incidence is likely to be higher. It is estimated that half of these familial cases may be due to inherited mutations in susceptibility genes [2–4]. In 1992, King et al. identified a locus on the long arm of chromosome 17 that had a high degree of linkage in families with a strong history of breast and ovarian cancer [5], and 2 years later Skolnick et al. identified the BRCA-1 gene at that locus [6]. This was the first adult-onset cancer to be mapped to a single gene locus, and in 1995 a second gene was identified, called BRCA-2. These two genes are probably responsible for up to 90% of all inherited breast cancers, and their discovery has ushered in the era of genetic susceptibility testing for breast cancer.

The clinical benefit of these discoveries seemed obvious. The potential hazards were less clear. The pressure to translate the scientific advances into effective strategies for cancer prevention or control has been considerable. The issues confronting the surgeon faced with a patient requesting genetic testing are coming to the forefront of clinical practice. In this review, we will summarize the knowledge of inherited susceptibility to breast cancer, examine recent information relating to BRCA-1 and -2 testing, and suggest guidelines for the surgeon faced with common clinical scenarios involving patients before and after they have been tested.

HEREDITARY BREAST CANCER SYNDROMES/SUSCEPTIBILITY GENES

A number of syndromes have been described that include an increased likelihood of developing breast cancer, often premenopausally, and occasionally bilaterally. The recognition of these syndromes has been the result of studies of pedigrees of cancer-prone families. Those that involve BRCA-1 or -2 represent the majority of these cases and will be the main focus of this review.

The breast-ovarian cancer syndrome, first described by Lynch and Krush in 1971 [7], describes families with early onset of both breast and ovarian cancer. Members of these families have a breast cancer risk of up to 50%, and about a 16% risk for ovarian cancer. BRCA-1 is the susceptibility gene responsible for this syndrome. BRCA-2 is responsible for many of the pedigrees in which there is a high incidence of breast cancer, but appears to have limited impact on ovarian cancer rates.

The Li-Fraumeni syndrome is due to an inherited mutation in the tumor suppressor gene p53. These patients develop early-onset soft tissue and osteosarcomas, breast cancer, brain tumors, leukemias, and adrenocortical carcinomas [8,9]. Acquired p53 mutations are the most common genetic abnormality in human breast cancer. Germline p53 mutations are responsible for about 1% of breast cancers diagnosed before the age of 40 [10]. The rarity of Li-Fraumeni and the difficulties involved in analyzing p53 have prevented widespread testing for p53 mutations.

Cowden's syndrome involves multiple hamartomas, with intertriginous trichilemmomas, oral papillomatosis, and acral keratoses in association with breast cancer. Thyroid adenomas and gastrointestinal polyps are also common in Cowden's syndrome patients [11]. The true incidence has been difficult to determine, as the syndrome is not well recognized, and many cases probably remain undiagnosed. The responsible gene, PTEN, has recently been identified, which should allow a much better understanding of the condition [12].

Ataxia-telangiectasia (AT) is an autosomal recessive condition leading to cerebellar ataxia, telangiectasia, radiation sensitivity, and an increased incidence of malignant disease. Homozygotes are particularly prone to development of non-Hodgkin's lymphomas, and also have significant risk of breast cancer. It was reported that heterozygotes had a fivefold increased risk of breast cancer compared with the normal population [13]. Subsequent studies failed to confirm this association [14–16]. Larger scale studies are underway to investigate the AT gene further and its possible links to breast cancer.

Hereditary non-polyposis colon cancer (HNPCC) is due to mutations in the genes involved in repair of damaged DNA. The clinical syndrome is dominated by the occurrence of early colon cancer, but various other ma-

lignancies are common. These include endometrial, ovarian, and urinary tract cancers. Increased frequency of breast cancer has been reported, but not quantified [17] and molecular evidence that breast cancer may be an integral tumor in patients with HNPCC is also available [18].

BRCA-1 AND BRCA-2

Mutations in BRCA-1 and BRCA-2 account for about 90% of the cases of hereditary breast cancer. Understanding these genes promises to improve our management of these patients. The initial estimates of the risk of breast and ovarian cancer in carriers of a BRCA-1 mutation were derived from genetic linkage studies of patients with strong family histories. A BRCA-1 carrier had an 82–87% chance of developing breast cancer by the age of 70 and a 44% risk of ovarian cancer [19,20]. There was also a significant incidence of other cancers, in particular prostate and colon cancer, in BRCA-1-linked families [19]. Compared with BRCA-1, BRCA-2 mutations appeared to be associated with a substantially lower incidence of ovarian cancer [21,22]. BRCA-2 mutations confer an increased risk of male breast cancer as well.

Structure and Function

BRCA-1 is a classic tumor suppressor gene with an autosomal dominant mode of transmission. It is a large gene, with 22 coding exons spread over about 100 kb of genomic DNA. The main mRNA species is about 7.8 kb, and the predicted protein is also large, at 1,863 amino acids [6]. Mutations and polymorphisms have been found throughout the entire coding sequence[23]. This is important in the context of screening, as focusing on one particular area of the gene would miss many mutations. In addition, many of the polymorphisms will have no functional significance, and their discovery during genetic testing may cause unnecessary alarm. BRCA-2 is nearly twice as large as BRCA-1, with 26 coding exons distributed over 70 kb, an mRNA larger than 10 kb, and a predicted protein of 3,418 amino acids [24]. The proteins have no significant homology to any previously described protein.

The normal function of BRCA-1 and -2 has been the focus of intense research. The proteins made by both BRCA-1 and -2 have been found to associate with RAD1, a protein involved in repair of double-stranded DNA damage. Mice with mutations of the BRCA-2 gene are more sensitive than normal to radiation-induced DNA damage [25,26]. This suggests that patients with BRCA-associated tumors may respond differently to radiation therapy. A second potential function of BRCA-1 involves regulation of the cell cycle via the cyclin-dependent kinase inhibitor p21 [27].

Pathology

Information on clinical characteristics of BRCA-associated tumors is sparse. When compared with control tumors they were on average of higher grade (66% grade 3 for BRCA-1, 41% for BRCA-2, 36% for controls) [28]. The occurrence of invasive lobular cancer was not significantly different, but medullary or atypical medullary carcinoma was more frequent in BRCA-1 carriers than BRCA-2 carriers or controls (13% v 3% v 2%). There was less ductal carcinoma in situ (DCIS) associated with the BRCA-1 cancers than with the controls (41% v 56%), and LCIS was less common in familial cancers [28]. Another study found that while hereditary cancers were of higher grade, the BRCA-1 cancers had a lower recurrence rate and a trend towards lower death rates than other hereditary breast cancers. When compared with control cancers the BRCA-1 cancers fared no worse, while other hereditary cancers had poorer survival [29]. Significantly higher 5-year survival in BRCA-1 carriers has also been reported from Scotland, although there is no obvious explanation for this [30]. It would be premature to use BRCA-1 or BRCA-2 gene status as a prognostic indicator at this point in time.

Incidence of Mutations

All of the germline BRCA mutations identified to date have been inherited. This is in contradistinction to many inherited metabolic diseases, in which acquired mutations are common. The lack of sporadic mutations raises the probability of large ‘‘founder’’ effects. In any well-defined ethnic community there will be certain mutations common to that community, i.e., mutations that could theoretically be traced back to a single ‘‘founder.’’ This has a profound impact on potential approaches to population screening for mutations. Three specific founder mutations have been identified in Ashkenazi Jews (those of Eastern and Central European descent). The 185delAG and 5382insC mutations in BRCA-1 and the 6174delT mutation in BRCA-2 are present in 2% of Ashkenazi women [31–34]. The mutations in BRCA-1, especially the 185delAG mutation, has been implicated in about 20% of breast cancers arising in Ashkenazi women before the age of 40 [35,36]. BRCA-2 has not been implicated in early breast cancer to nearly the same extent [37]. When other ethnic groups have been studied, mutations unique to the culture have been identified [38].

Much of the information about cancer risks associated with BRCA mutations was derived from mutation carriers with a strong family history. An interesting study of Jewish men and women from the Washington area suggests that, in the general community, the risks to a carrier may be significantly lower. Of 5,318 volunteers, 120 (2.3%) had one of the three BRCA founder mutations. Personal and family cancer history data were used to

TABLE I. Clinical Scenarios With Estimated Risk of BRCA-1 Mutation of >10%

Patient history	Age criterion (yr)	Family history
Unilateral breast cancer	<45	Ovarian cancer
Bilateral breast cancer	<50	Breast cancer
Ovarian cancer	<50	
Unilateral breast cancer	<50	Ashkenazi

assess cancer risks. By this analysis, the risk of breast cancer by age 70 was 56%, that of ovarian cancer was 16%, that of prostate cancer was 16%, and there was no elevation in the risk of colon cancer [39]. A caveat to this study is that the figures for penetrance were derived from reported family histories and not from longitudinal follow-up. Another study using epidemiological data estimated that the risk of breast and ovarian cancer in BRCA-1 mutation carriers is 73.5% and 27.8% by age 80 [40]. Both these studies suggest that the risk of developing cancer may be lower than previous estimates, but it is important to note that the differences may not be statistically significant.

In order to understand the significance of BRCA mutations on breast surgical practice, the experience from ''high-risk clinics'' is valuable. Two recent series reported the full-length BRCA-1 sequence analysis of 263 and 798 unrelated women from high-risk clinics. Significant mutations were found in 16% and 13%, respectively [23,41]. From these data, groups of patients at high risk of carrying a BRCA-1 mutation can be identified. A personal history of unilateral breast cancer, bilateral breast cancer, ovarian cancer alone, ovarian cancer in association with unilateral breast, and finally ovarian and bilateral breast cancer are associated with an increasing risk of BRCA-1 mutation. For family history, each relative with breast and ovarian cancer conveys a greater risk than those with ovarian cancer alone, or with breast cancer alone. Young age of diagnosis in both patient and affected family member is significant [23]. Table I shows the minimum combination of age of onset and family history that would imply a 10% risk of a mutation. The combination of age of diagnosis and extent of family history can be used to calculate an approximate risk of mutation.

It is important to understand the limitations of current genetic testing techniques. Myriad Genetics (Salt Lake City, UT, the nation's largest commercial testing organization) uses polymerase chain reaction (PCR) amplification and sequencing of the entire coding sequence. This technique is unable to detect alterations in the regulatory sequences that might alter gene expression. It requires amplification of both alleles and does not detect either mutations or deletions that alter the PCR primer binding sites; therefore large genomic deletions would also be missed. A recent study from The Netherlands found that about one-third of the mutations identified in Dutch breast cancer families involve large deletions that escape detection by PCR-based mutation screening methods [38]. This highlights the incomplete nature of our present knowledge and reinforces our need to be aware that negative tests may not be conclusive, and that different ethnic populations will have different mutation spectra from those initially studied. Myriad Genetics estimates that current technologies miss 5–15% of significant mutations [23].

CLINICAL IMPACT OF GENETIC TESTING

Testing for susceptibility to breast cancer is most valuable when the result affects patient management. The ideal intervention would completely prevent the development of the cancer without potential for physical or psychological morbidity. Unfortunately the primary prevention of breast cancer remains an ideal. Prophylactic mastectomy remains the only currently available modality to reduce breast cancer risk. Anatomical studies have demonstrated that it is virtually impossible to remove all breast tissue surgically [42]. In particular, the nipple-sparing subcutaneous mastectomy via inframammary incisions is estimated to leave about 5–15% of breast tissue [43]. Numerous reports document breast cancer after prophylactic surgery [44,45], but no good overall outcome data are available. Our group has established a National Prophylactic Mastectomy Registry to begin to address this controversial procedure. We have gathered data on over 1,000 women across the nation who have undergone prophylactic breast surgery. We hope that this Registry will provide valuable information about prophylactic mastectomy, especially in the context of genetic predisposition.

Trials of tamoxifen as a (putative) chemo-preventative agent are under way in the United States and internationally. The National Surgical and Adjuvant Breast Project (NSAPB) began accruing patients in 1992 for a prospective trial comparing tamoxifen against control for the prevention of breast cancer in all women over 60, and in younger women at high risk for developing breast cancer. Results are likely to be available in 2–3 years. A key point will be the drug's effectiveness in the high-risk (genetically predisposed) population.

Oral contraception and prophylactic oophorectomy are options for primary prevention of ovarian cancer. Oral contraceptives have been shown to reduce the risk of ovarian cancer by up to 50% after 5 years of use [46], but there are no data on its effectiveness in high-risk women. Prophylactic oophorectomy does not eliminate the risk of ovarian cancer, as primary peritoneal carcinoma (PPC; (histopathologically indistinguishable form ovarian carcinoma) can occur after oophorectomy. The incidence of PPC has been reported to be between 2% and 10%, occurring 1–27 years after the prophylactic surgery [47,48].

As only about one-half of these patients would have been mutation carriers, it is reasonable to assume that the incidence in mutation carriers would be between 4% and 20%. In a small prospective study of high-risk people undergoing oophorectomy that used siblings as controls, the incidence of ovarian carcinoma was reduced by about 50% [49]. The risk of ovarian cancer in carriers of BRCA-1 is low before the age of 40, so if chosen, oophorectomy may be safely delayed until after childbearing is complete; and hormone replacement therapy should attenuate the morbidity of early menopause.

A study of the potential impact of prophylactic surgery on life expectancy in women carrying BRCA mutations concluded that prophylactic mastectomy offers substantial gains in life expectancy, and oophorectomy more limited gains [50]. Such an analysis depends on many assumptions, in particular on estimates of the cumulative risk of breast and ovarian cancer in mutation carriers, of the effectiveness of prophylactic surgery, and of the survivability of breast and ovarian cancer. If the risk estimates from the breast cancer linkage consortium were used (87% risk of breast cancer and 40% incidence of ovarian cancer by age 70)[19,20], the estimated gain in life expectancy was 7.6 years for prophylactic mastectomy and oophorectomy at age 30 and 7.2 years if the oophorectomy was delayed until age 40. If the mean risk from the Washington area study were used [39], the equivalent figures were 5.3 and 5.1 years. If mastectomy and oophorectomy were performed at age 60, the estimated gain in life expectancy was 0.9 or 0.4 years depending on the assumptions. The authors chose to be very conservative in estimating the impact of prophylactic surgery on risk reduction (85% for prophylactic mastectomy and 50% for prophylactic oophorectomy) and chose a study of BRCA-1 carriers with ovarian cancer in which the outcome was highly favorable [51]. Both of these assumption would reduce the potential benefit of prophylactic surgery. The 50% reduction in ovarian cancer after oophorectomy [49] has been questioned. Using the 4% incidence of peritoneal adenocarcinoma calculated from the Gilda Radner Familial Ovarian Cancer Registry report [47] the risk reduction estimate becomes 75–90%. The survival figures quoted by Rubin et al. [51] have been disputed due to the lack of accurate disease subsetting in the two groups and differences in treatment approaches between mutation carriers and controls [52,53]. This study is a valuable starting point and highlights that even with conservative assumptions, prophylactic surgery has a significant potential impact on inherited carriers. Translating this into clinical management of individual patients is problematic.

Access to Testing—the Dilemma

In February 1996, the American Society of Clinical Oncology (ASCO) issued a statement regarding the appropriate use of genetic testing for cancer susceptibility in response to concern that uncontrolled access to testing could be harmful. ASCO recommended that testing should be done after full informed consent with pre- and post-test counseling, and in the context of long-term outcome studies whenever possible. The only people who should be considered for testing are those with a reasonable likelihood of the test being positive, and for whom the test result could alter their medical management. They also support regulation of the testing laboratories and legislation to prevent discrimination based on the test results [54].

Both the National Action Plan on Breast Cancer (NAPB) and the National Breast Cancer Coalition supported the general thrust of the ASCO statement, with the latter group urging that testing be available only to individuals who agree to join peer-reviewed, approved research protocols [55,56].

Test providers point out that many women want to be tested. They recognize that our knowledge is incomplete and that incorporating testing into clinical practice has potential problems, but they imply that these are insufficient grounds for withholding of information [57]. They argue that prevention is better than cure and that early diagnosis is better than late diagnosis and assume that genetic predisposition testing will aid in both prevention and early diagnosis. Insisting on further research before recommending widespread screening or suggesting that it should not be a decision for the patient alone is seen as unduly cautious or paternalistic [58].

This is not a debate confined to medical journals. Patient advocacy groups were involved in the ASCO statement, and genetic testing is a regular topic in the popular press. Arguments for ready availability of testing are based on the right of the patient to information and frequently assume that the benefits outweigh the risks. Even if the benefits are not clear-cut, suggestions that decisions about testing should be taken from women are condemned. Articles urging caution focus on our incomplete understanding of the role of the susceptibility genes in carcinogenesis with consequent incomplete understanding of the significance of a positive or negative test.

Potential Risks of Testing

The potential downside of genetic testing must be considered. While it might be considered paternalistic to deny access to testing because of perceived risks, it is irresponsible to encourage testing without exploring the potential consequences.

The psychological impact of a diagnosis of breast cancer can be devastating. The psychological effects of testing for breast cancer susceptibility are inadequately understood, but parental guilt, depression after a positive test, and ''survivor guilt'' after a negative test do occur. Dr. Lynch reported anecdotal accounts of typical re-

sponses in women from hereditary breast and breast-ovarian cancer-prone families. Most involved fear and anxiety, but sometimes also involved denial and depression. It is crucial for those involved with the care of the high-risk individual to consider the patient's psychological well-being [59]. A prospective study of 279 people with BRCA-1-linked hereditary breast or ovarian cancer found that 1 month after receiving the BRCA-1 test results, individuals identified as mutation carriers (n = 53) did not exhibit increases, but those identified as non-carriers (n = 62) showed statistically significant reductions in depression or functional impairment compared with those not tested [60]. Further studies are needed on the psychological impact of mutation testing.

From the patient's point of view, a much more concrete and worrying issue is that of the financial ramifications of being tested, particularly if the test is positive. In people being tested for inherited metabolic diseases, 25% believed they were refused life insurance, 22% health insurance, and 13% believed they were refused or let go from a job [61]. Fear of similar discrimination after genetic testing for cancer susceptibility is a major reason given for not being tested when the indications appear clear (K. Offit, personal communication). We are not aware of any cases of insurance or employment discrimination associated with genetic testing for breast cancer. Recently, an insurance company executive was quoted: ''We oppose any prohibition on the ability to collect information for risk assessment and risk selection.'' From a purely financial standpoint this is quite reasonable, but it raises the prospect of the creation of a genetic underclass, who might be virtually uninsurable. The ASCO statement recognized this concern, and supported legislation to outlaw discrimination on the basis of genetic characteristics. Various pieces of legislation have been formulated, and at the time of writing, at least 24 states have enacted laws providing some protection against abuse of genetic information in an insurance or employment setting. In a number of states, bills that had promised additional protection have been defeated. At the national level, President Clinton recently endorsed a bill that would protect women undergoing genetic testing for breast cancer (Snowe-Slaughter, House of Representatives Bill 306 and Senate Bill 89, 1997).

Clinical Scenarios

The surgeon is faced with the issue of genetic testing in different clinical situations. These include the patient with breast cancer and at high risk of carrying a mutation, the person without disease whose family has a known mutation, and the person without disease but with a suggestive family history. The over-riding issue when deciding whether or not to test in each of these situations is ''Would the test result alter the medical management?''

For the patient with breast cancer, the issues relate to management of the contralateral breast— whether to use normal surveillance, or whether to contemplate prophylactic contralateral mastectomy. The contralateral breast cancer development rate in BRCA-1 heterozygotes exceeds 60% [62]. This is important if the patient is undergoing mastectomy with TRAM reconstruction, which can only be performed once. If a BRCA-1 mutation is present, prophylactic oophorectomy should also be considered.

For the person without disease but with a known family history of a mutation in an affected family member, clarifying mutation status could clearly identify the patient's risk category and might help her decide on special surveillance, prophylactic surgery, or possibly chemoprevention.

The person without disease but a suggestive family history is more difficult. The impact of a positive result is similar to that for a known mutation, in that it would help to make a decision about surveillance and/or prophylaxis. A negative test in this situation is of marginal value, however, because distinguishing a false negative from a true negative is impossible.

Before testing occurs, informed consent is mandatory. In New York State, legislation prohibits genetic testing without counseling about the various issues outlined above and without informed consent. All potential candidates for testing at Memorial Hospital consult with a clinical cancer geneticist and counselor. The medical, psychological, social, and financial impact of both a positive and a negative test are discussed, and decisions about testing are usually deferred to a later consultation. After consideration of all the issues, only about 40% of those referred to genetic counseling eventually undergo testing. Concern about the potential for financial sequelae is the most common reason given for deferral.

CONCLUSIONS

The discovery of the genes responsible for most hereditary breast cancers is without doubt a major breakthrough and will eventually lead to improved care for those women who belong to affected families. Because current knowledge is continually changing, it is not wise to make blanket policies regarding the implementation of genetic testing. As surgeons involved in the day to day care of patients who may be at risk of carrying these mutations, we need to be aware that the situation is complex and that each person presents with a different set of medical, ethical, religious, social, and financial circumstances that require us to adopt an individualized approach. It is crucial to explore with the patient whether the test result is worth the exposure to the potential risks and costs. As our knowledge of the significance of various mutations in various clinical settings improves, and as we assess the impact of various preventative and therapeutic strategies, the impact of the tests on outcome

should become clear. In addition, as further legislative steps are (hopefully) taken to reduce the risk of genetic discrimination, another potential disincentive to testing will have been removed. Psychological issues will always remain and they mandate that we approach the issue with due sensitivity.

These discoveries have moved us into a new era in the diagnosis and treatment of breast cancer. They have created a new type of patient—the nonpatient—who seeks intervention based on what might happen rather than on what has happened. They have revealed ethical, social, and psychological issues that have not previously been in the domain of the surgical practice. They may expose patients to risks, many of which we cannot predict. Despite these concerns, this new information holds great promise for moving us from a purely descriptive understanding of the disease to a functional one. It is critical that the surgeon continue to play a central role as these discoveries are translated into the prevention, diagnosis, and treatment of breast cancer.

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